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- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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10 February 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FRAGMENTS OF PROINSULIN C-PEPTIDE

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(57) Abstract: The present invention relates to peptides being the N-terminal fragment of human proinsulin C-peptide and having the sequence EAEDLQVGQVEL (SEQ ID No: 2) or a fragment or peptide derivative thereof retaining the functional ability of the N-terminal fragment to contribute to C-peptide activity, wherein said fragment or peptide derivative comprises two acidic amino acid residues and is capable of adopting a conformation where said two acidic amino acid residues are spatially separated from one another by a distance of 9-14 Å between the α-carbons thereof; and wherein said peptide derivative does not include native C-peptide of any species nor human C-peptide 1-15, 1-24 or 1-26 or rat C-peptide 1-26. The invention also relates to peptides having an amino acid sequence comprising (i) the N-terminal fragment of human insulin C-peptide having the sequence EAEDLQVGQVEL (SEQ ID NO. 2) or (ii) a fragment or peptide derivative of amino acid sequence SEQ ID NO. 2 retaining the functional ability of said N-terminal fragment to contribute to C-peptide activity, wherein said fragment or peptide derivative comprises two acidic amino acid residues and is capable of adopting a conformation wherein said two acidic amino acid residues are spatially separated from one another by a distance of 9-14 Å between the α-α-carbons thereof; said peptide having C-peptide activity, but not including native C-peptide of any species nor human C-peptide 1-15, 1-24 or des 13-17. The invention further relates to peptides having the formula Xn-Y-Xm-Y-Xp where X is any amino acid, Y is an acidic amino acid, n=0-6, m=5-9 and p=0-6. First and second medical indications, pharmaceutical compositions and products for use as a combined preparation are also covered by the present invention.

INTERNATIONAL SEARCH REPORT

International Application No
/GB 03/03571

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07K14/62 A61K38/28 A61P5/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | WO 00/12679 A (UNIV NEW YORK) 9 March 2000 (2000-03-09) sequence 84 ----- | 1-16 |
| X | IDO, Y. ET AL: "Prevention of vascular and neural dysfunction in diabetic rats by C-peptide Prevention of vascular and neural dysfunction in diabetic rats by C-peptide" SCIENCE (WASHINGTON, D. C.) , 277, 563-566 CODEN: SCIEAS; ISSN: 0036-8075, 25 July 1997 (1997-07-25), XP002298804 figure 3 ----- -/- | 1-25 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

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10/12/2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | NARITA, MITSUAKI ET AL: "Design of the synthetic route for peptides and proteins based on the solubility prediction method. I. Synthesis and solubility properties of human proinsulin C-peptide fragments Design of the synthetic route for peptides and proteins based on the solubility prediction method. I. Synthesis and so" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN , 59(8), 2433-8 CODEN: BCSJA8; ISSN: 0009-2673, 1986, XP008036262 figure 1 | 1-9, 11-14 |

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

Present claims 1-2 relate to a compound defined by reference to a desirable property, namely the functional ability of the N-terminus of the insulin C-peptide. Claims 15 and 16 relate to the first medical use of such a compound.

The claims 1-2 furthermore relate to the desirable property, namely being able to adopt a conformation wherein two acidic amino acids are spatially separated by a distance of 9-14. Claims 15 and 16 relate to the first medical use of such a compound.

Claims 6, 8, 10 and 14 are dependent to claims 1 or 2 and introduce more desirable properties, namely that the peptide of invention is capable to adopt an α -helical conformation (claim 6), or that the helix presents a conserved surface after addition of further amino acids to the peptides (claim 8) or that the two acidic amino acids within the claimed peptide are capable of interacting with a third acidic amino acid (claim 10) or that said two acidic amino acids are separated by 10-13 (claim 14).

Claims 15 and 16 relate to the first medical use of such a compound.

The claims cover all compounds having these properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such compounds. In the present case, the claims so lack support and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in the examples and closely related ones.

The International Search Authority considered the term 'does not include native C-peptide of any species' used in claims 1,2,15 and 16 to be vague and unclear and thus leaving the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

overcome.

INTERNATIONAL SEARCH REPORT

National Application No

/GB 03/03571

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|--------------|------------------|
| WO 0012679 | A 09-03-2000 | AU | 767507 B2 | 13-11-2003 |
| | | AU | 5586999 A | 21-03-2000 |
| | | CA | 2341064 A1 | 09-03-2000 |
| | | EP | 1108008 A1 | 20-06-2001 |
| | | JP | 2003512008 T | 02-04-2003 |
| | | NZ | 510312 A | 30-01-2004 |
| | | NZ | 529720 A | 19-12-2003 |
| | | WO | 0012679 A1 | 09-03-2000 |
| | | US | 6720181 B1 | 13-04-2004 |